Assuring the Benefits of Immunization in the Future: Research in the Public Interest

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INTRODUCTION

A reasonable way to begin predicting the future of biologicals is to examine critical elements in their past. We have chosen to consider the evolution of biologicals and of what we call the "biologicals enterprise" in terms of prevailing human needs, scientific possibilities, and sociocultural attitudes. We hope to persuade you that the biologicals enterprise has become a public responsibility of national and international proportion. As such, we believe its future well-being requires specific, identifiable support and participation by the public.

BIOLOGICALS: PAST, PRESENT, AND FUTURE

It is hard to tell exactly when anything akin to a modern biological was first used. The Ebers Papyrus dating from about 1550 B.C. describes "simples" of the day, medicaments of varied sorts, that contained blood, excreta, fats, and visceral parts of birds, mammals, and reptiles(*1*). Whether they would qualify as "biologicals" is highly doubtful; that they were immunogenic is not likely to be questioned.

Preparations reasonably termed "biologicals"—in today's definition, at least—have all been developed in the last two centuries, most of them in the last fifty years or less. The first one, smallpox vaccine, was essentially a natural product: vaccinia virus, the etiologic agent of cowpox, that usually caused only localized disease in humans but rendered them smallpox-immune.

By contrast, recently-developed biologicals have become carefully-manipulated, highly-sophisticated products, incorporating all the scientific insights and skills of contemporary microbiology, immunology, and, if you will, vaccinology(*2*). Each new product to be developed has undergone progressively more meticulous "bench-phase" study, extensive field testing, and in-use surveillance of potency, effectiveness, benefits, and risks.

Development Timetables

One approximation of the increasing complexity of biologicals has been the lengthening interval between a vaccine's conception and its reasonably general use. Two of the most important factors controlling the time of development involve scientific validation and assurances of safety.

The timetable for developing the biologicals that appeared late in the 19th century is not well documented. The process seemingly was rapid. Vaccines which were merely killed cultures of microorganisms like the cholera vibrio and the plague bacillus—after some preliminary tests of their protective capabilities in animals—were readily injected into volunteers, the vaccine developer commonly being one of them. A year or less may have elapsed between bench and clinical trial. In

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those days, the scientist's own judgment was the principal determinant of when to proceed. There were, as yet, no standardized safety, purity, or potency requirements to be met in advance of vaccine distribution. There were, however, and important to our inquiry, retrospective evaluation and often severely critical scientific debate by peers.

In 1897, Haffkine, a pupil of Pasteur, prepared a vaccine of killed plague bacilli and observed that it protected animals against inoculation of virulent cultures. He promptly proceeded to inoculate himself and several hundred volunteers—the number growing to more than 8,000 in a few weeks. The vaccine proved to be moderately effective, and in 1902-03, more than half a million people received it in Mulkowal, India, during an epidemic(3).[a]

Not only heightened scientific goals but also enhanced concern for human safety resulted in lengthening the gestation period of biologicals. There are numerous examples where failure to conduct thorough pre-clinical tests before beginning trials in humans endangered the lives of study participants and resulted in scientific censure and public outcry. For example, in the United States in the 1930's, Kolmer and Brodie, working independently (and somewhat in competition), both hastily began human clinical trials with what were believed to be "inactivated" poliovirus antigens without having conducted adequate safety tests beforehand in animals. Paralytic poliomyelitis occurred in at least 12 of the approximately 10,000 persons injected. Both vaccines were subsequently discredited and permanently withdrawn from use(4). The adverse impact of these trials—undertaken quite prematurely—delayed progress in polio vaccine development for nearly 20 years. Scientific and public reaction to the disaster demanded greater stringency in evaluating candidate vaccines for eventual human clinical trial.

At the present time, years are required for pre-use testing to assure safety and demonstrate effectiveness. Granted there may have been less inherent complexity and risk of the killed vaccines of the late 19th century than in the attenuated virus antigens which constitute many of our newer vaccines. Still, recently-licensed vaccines like those against measles, mumps, and rubella remained under development and testing for up to 10 years from the time prototype antigens were prepared until they were licensed and generally available.

Need, Possibility, and Acceptability

The process determining which biologicals came into being was a synthesis of what was needed to control or prevent important human diseases, what was possible in terms of existing scientific and technical knowledge, and what was acceptable with respect to relative value. Most vaccine efforts were in response to disease problems of general and worldwide importance. Others, however, addressed needs of special populations and limited geographies.

Jenner's observations on the coxpox-smallpox interrelationship and his famous "one-child" experiment with 8-year-old James Phipps (1796) launched extensive, but not unchallenged, use and evaluation of smallpox vaccine, ultimately the first practical biological(5). By 1976, its systematic use has nearly eliminated one of the world's greatest disease problems.

The next major biological advance was Pasteur's post-exposure treatment of rabies, a uniformly fatal disease. This involved far more intricate scientific manipulations than had Jenner's effort. Pasteur developed a vaccine composed of rabies-infected rabbit spinal cords, dessicated to "attenuate" the causative agent. Its use—first, and successful, in 9-year-old Joseph Meister (1885)—resulted in great opposition from leading physicians on scientific and ethical grounds. Pasteur's career was, at

[a]Unfortunately, tragedy marred its use: The laboratory producing Haffkine's vaccine, pressed by demands from the field, lowered its standards, and tetanus spores contaminated some lots. There were 19 deaths from tetanus.

least temporarily, threatened by persisting in rabies vaccine work(6).

In subsequent years, the development of biologicals occurred at a rate and in a number directly proportional to the growth of potentially contributing fields. Pasteur, Koch, Ehrlich, and their contemporaries explored and described fundamental microbiological and immunological principles to sufficient degree that by the beginning of the 20th century, much of the groundwork had been laid for preparing killed bacterial vaccines and toxoids of diphtheria and tetanus. This knowledge coupled with modern achievements of science and technology have resulted in the development of nearly 25 important vaccines for human use.

Besides the large number of today's general-use biologicals like smallpox, polio, and yellow fever vaccines and immune serum and hyperimmune human globulins, others have been developed for specialized purposes. Individuals or groups at high risk of exposure by virtue of age, occupation, avocation, travel, or geography now have access to a variety of effective biologicals, many of recent vintage: botulinum toxoid for certain industrial or laboratory workers, antivenins and tularemia vaccine for persons who might have specific animal contacts, meningococcal and arbovirus vaccines for populations or communities particularly vulnerable to such infections or for those facing an epidemic.

In the future as in the past, scientific capabilities will be major determinants of biologicals' progress. Contributing to it already are such technologies as genetic alteration of microorganisms, immunochemistry of antigens, and advanced electron microscopy. These and yet unthought of advances should move us closer to ultimately solving many of the world's disease problems through immunization.

Before leaving our survey of scientific achievements from which biologicals emerged, it should be noted that discoveries other than those of the biological sciences stimulated development and use of vaccines. Take, for example, invention of the hypodermic needle and syringe (mid-19th century)(7). Parenteral injection led not only to more precise research efforts but also to general use of injectable antigens. The jet injection apparatus of the mid-20th century did even more to stimulate mass immunization programs.

Field Testing

A critical phase of developing biologicals is the human clinical trial or field test. In that it involves human participants, it is especially pertinent to our review. Only in clinical trials can some of the most important characteristics of biologicals be determined. These involve human safety, potency, and effectiveness.

Effectiveness trials of biologicals have almost always been designed to evaluate individual protection against natural disease challenge. The Medical Research Council (MRC) (United Kingdom) trials of pertussis vaccines were among the first large-scale studies designed specifically to determine effectiveness. These trials, begun in the 1940's, were important because they incorporated a number of guiding principles, marking a new era in field trial design: a) adequate pre-clinical data on safety, adverse reactions, and effectiveness; b) pilot trial before large-scale field trial; c) concept of two identical groups, a "test" and a "control" group; d) blind observation; e) uniform diagnostic criteria; f) fully-informed consent; g) geographical representation; and h) termination when data are statistically significant(8).

In the United States in 1954, a monumental clinical trial of a newly developed inactivated poliomyelitis vaccine incorporated the MRC concepts. The so-called "Francis Field Trial" was sponsored by the National Foundation for Infantile Paralysis. Adequate pre-clinical studies had been conducted, study design had been carefully reviewed, the trial was to be intensively monitored, and large numbers of persons (more than 1.8 million) in the appropriate "target population" were involved. Both a "placebo" and an "observational control" group were to be studied. Adequate

geographical and socio-economic representation were included, every effort was made to obtain truly informed consent, and the study was not to be extended past the point of statistical significance between vaccinated and control groups. The results gave clear evidence of the vaccine's safety and effectiveness.[a]

Thus, by the mid-20th century, highly sophisticated clinical field trials were being conducted. Notable have been efforts to conduct specific trials in age groups in which vaccination is expected to be principally recommended. (Prohibitions or cautions on trials in children are confounding this valuable objective.) As with the earliest evaluation of biologicals in humans, however, objectives continued to be demonstration of individual protection. Field tests have not systematically addressed the question of the effectiveness of biologicals in protecting the community.

Community Trials

Biologicals have two distinctive but related actions in preventing communicable diseases. One is to protect individuals by immunizing them; the other is to protect groups of individuals—classically "herds"—to the extent that effectively immunized members of the groups do not become ill and thereby do not infect susceptible contacts. Without belaboring a well-worn concept of basic epidemiology, population- or community-oriented preventive medicine strategies rely on the immunized portion to reduce or eliminate the chance that communicable diseases will spread. (If you will, the immunes protect the susceptibles.)

To provide us with the full range of information needed to judge the usefulness of a biological, we should be able to forecast its value for the community. To do so, we need to address issues such as the duration of vaccine effectiveness, the influence of vaccination on the natural history of disease, the ability of biologicals to protect against infection as opposed to illness, and the low-level or rare risks associated with widespread use. As a result of vaccine field trials conducted in the past, biologicals have been used with little and often imprecise knowledge of their value in a community or population context. The sorts of questions asked about community effectiveness have been answered only after vaccines were licensed and in general use. Often, even then, indirect evidence and uncontrolled observations of effectiveness were all that were available to evaluate vaccine performance and develop strategies for use.

It has become increasingly clear, that before recommending vaccines, not only their value for individuals but also for groups or communities should be better understood. This will require that field trials be designed for a "natural community," an ecological unit rather than a contrived population. Furthermore, in being a natural community, we recognize that adequate trials will involve not only participants in the trial (the treated and the untreated or controls) but also those who choose not to take part—the non-volunteers, if you wish. (Matters of protocol design and informed consent for natural community trials, particularly addressing the important non-participant issue, will need to be considered carefully.)

The Biologicals Enterprise

At some ill-defined time in the evolution of efforts to produce safe and effective biologicals—a recent time, to be sure—the process gradually underwent an important change. That change involved transforming a private, scientist-oriented research activity into a publicly-committed enterprise. It involved amending standards of science and ethics for investigators by requiring compliance with national and international codes, regulations, and licensing procedures. It involved incorporating demands for safety, potency, and

a. "Evaluation of the 1954 Field Trial of Poliomyelitis Vaccine." Final report by the Poliomyelitis Vaccine Evaluation Center, Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan, April 1957.

effectiveness set down not only by scientific peers but also by public agencies.[a]

In essence, in response to dependency on its products, the biologicals research and development effort became a "public interest" responsibility. Its output became a concern of community, national, and international groups responsible for controlling vaccine-preventable diseases and eliminating spread across jurisdictional boundaries. The use of biologicals came to play a major role in the strategies for assuring the health of the public as part of and in addition to assuring the health of individuals.

A useful way to characterize the biologicals enterprise is to borrow a concept from the economists. This involves what are known by them as "public goods." Public goods, like national defense, fire protection, or public roads, are available to and consumed by all the public. In a sense they belong to the public and cannot be withheld from those who choose not to support them. Public goods involve governmental expenditures on behalf of the public(9). In that the public's health and well-being are goods enjoyed by all, biologicals, as determinants of health, can reasonably claim a place among the public's health resources.

The reason for calling attention to an economic concept is that it helps underscore a major conclusion of our review of biologicals. That is that society, the people, as major beneficiaries of the biologicals enterprise, have a collective stake in and responsibility for its existence. Economists, like epidemiologists, would acknowledge the reliance which population groups as well as individuals have come to place on biologicals for disease prevention and control.

WHAT OF THE FUTURE

It is reasonable to assume that what shaped the current enterprise of biologicals research, development, and use will exert the major influences on its future. We have chosen two words to describe how we expect the future to look. Our choices are "deliberate" and "democratized."

By "deliberate" we want to suggest that in the future, the biologicals effort will represent more forthright and systematic strategies of research, development, and use than is now the case. These can be expected to represent consensus opinions from therapeutic and preventive medical and public perspectives as to what is high priority and what is scientifically possible, economically affordable, and acceptable in practice.

The goals for future biologicals will probably be both general-use products for currently unpreventable or poorly preventable diseases of worldwide importance (for example, syphilis, gonorrhea, schistosomiasis, malaria) and "targeted" biologicals for high risk groups in limited locales (for example, onchocerciasis, hepatitis B, Lassa fever, certain human cancers).

Characterizing the future of biologicals as "deliberate" is not to suggest there is no current direction in the field. There is, of course, a great awareness of the human needs which biologicals might address, and there is certainly full exploitation of available science. Rather, what we want to indicate is essentially an enlarged body of consensus judgment about priorities and resources, often international in scope. This viewpoint comes from recognizing that the problems to be addressed in the future, including the financial and human resources to solve them, supersede any single nation's needs and capabilities. Take influenza as an example.

Influenza is an international disease with pandemic and epidemic potentialities. It is one from which hundreds of millions of people become ill and millions die. It has a complex natural history, largely the result of its being caused by genetically labile viruses.

[a] Governmental supervision and regulation of biologicals exist in most countries. Legislative authorities for control began to appear early in the 20th Century: United States, Food and Drug Act of 1906; United Kingdom, Therapeutic Substances Act of 1925; etc. International efforts began with the appointment of a Permanent Commission on Biological Standardization by the Health Commission of the League of Nations (1929), the World Health Organization continues this function.

Consequently, inactivated influenza vaccines—the most generally used preventives, first conceived about 30 years ago—need regular updating, often annual, so they approximately "match" the viruses expected to be prevalent. This process is inexact at best, and resulting vaccines have been only variably useful.

Current influenza prevention and control efforts rely heavily on international cooperation in surveillance of viruses and trials of recommended vaccines. To progress beyond the current phase of what must be acknowledged as generally ineffective influenza control, we will need an even more deliberate effort to detect virus variants at the earliest moment, to pool scientific concepts of influenza's immunology and vaccinology, and to evaluate the ability of vaccines or other preventives, in fact, to influence the spread and impact of the disease among the world's communities. This will require advance planning and collaboration on protocols deliberately designed for statistically valid results in community trials.

By characterizing the biologicals enterprise of the future as "democratized," we want to suggest that it will involve progressively more peer and societal involvement. This forecast relates to setting priorities, evaluating scientific feasibility, providing funds, recommending uses, and generally participating in all phases of the effort. To anyone whose interests touch on science, medicine, law, ethics, sociology, or other disciplines in which the rights and privileges of individuals are involved, "democratized" would seem to be a reasonably key word.

The past decade or two have seen the emergence of a new public assertiveness of individual rights in many countries of the world. In the United States, it has been called the "consumer movement." Consumerism, however, is too narrow a concept, since what has been seen is public expression of a desire or a demand to influence and be active in whatever is happening to society. This has led, as we are all aware, to far-reaching statutes and court opinions on social justice, to regulations controlling research involving human subjects, to a required public participation in many policy-making activities, and to broad rulings on freedom of information, rights of personal privacy, and open forums.

Complicating the public's activism with respect to health and biomedical research is a growing indifference or even antagonism between the public and research. On the one hand, there seems to be public confidence that useful goods and services for health will flow indefinitely from ill-defined sources. With specific reference to biologicals, the licensing and general use in the United States of about ten new vaccines and various hyperimmune globulins of human origin in the past two decades as well as publicity for vaccines under test (for example, hepatitis B and varicella vaccines and hepatitis B immune globulin) have led the public to expect that most common health problems are merely awaiting their turn for a biologicals solution—cancer notwithstanding.

On the other hand, and compounding the public's misconception of its collective role, there is mounting suspicion that motivations in research are largely self-serving. There has been outrage over the use of human subjects in some clinical trials, alarm over the inherent risk of biologicals as a result of litigation of personal injury claims, prohibition or suppression of some classes of research involving humans, and claims of general failure to apply the output of science to solving the fundamental problems of contemporary life.[a] Although the public's indifference to or antagonism with research many have arisen from examples of

[a] In the United States a National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was created in 1974 to review the mechanisms for protecting research subjects and to propose, if needed, more suitable controls and procedures. The Commission was charged to rule on controversial issues such as fetal and pregnancy research and research involving children, institutionalized patients, and prisoners with regard to their suitability for involvement in field tests and pre-licensing studies of drugs.

acknowledged shortcomings or even abuses, current sociocultural attitudes and legal liability issues could seriously hamper or essentially paralyze progress in biologicals research and development unless counteracted.

Our characterizing the future as "deliberate" and "democratized" might seem to some observers to threaten the basic principles of free and imaginative research. It might seem to bureaucratize the developmental and utilization phases of biologicals. These cautioning interpretations, we believe, are not entirely justified. In fact, we submit that by expecting more aggressive societal involvement in the biologicals effort and awareness of its being a public interest investment, our forecast might actually envision enhanced support of its research, development, and use.

What does cause us concern in describing the future of biologicals as we have, however, is the lack of useful mechanisms by which this future can be helped to appear. There currently are few or no ways that society, *per se*, can set reasonable priorities or provide support or take part in research deemed good for the public. Elective processes—scientific or governmental—are ill-equipped to do it. And yet, they are the generally-accepted mechanisms for implementing public choices. Politicians, it would seem, should not be expected to adequately assess health needs, evaluate scientific-technical possibilities, or represent the public by participating in the biologicals initiative.

RESEARCH IN THE PUBLIC INTEREST

How, then, can we help to assure a desirable future for the biologicals enterprise. One way, we believe, is to call for clear recognition of the public's dependence on research undertaken directly in its own behalf. This could be stimulated by specifically designating such research as a special category—"research in the public interest." For biologicals, this would mean distinguishing their basic research and development efforts from those oriented toward personal health goals like disease therapy, in which the public at large can expect little collective benefit.

We might define research in the public interest as "that part of the total research effort of which the principal beneficiary is the public, not the individual, and, thereby, in which the public has a special duty to encourage, financially support, and participate."

There are obvious benefits in designating a category of public interest research. For one, the concept could assist research planning and budgeting. Research efforts are internally competitive, and within various scientific areas, the best proposals are given priority support. In times of economic stringencies, the competition is great. The concept of research in the public interest applied to certain lines of research would help distinguish projects potentially meritorious for the public good. Scientists, health professionals, legislators, administrators, and the public itself could more clearly direct their support toward efforts identified with the public good. The concept should not be seen as a plea for special privileges but rather for special identification.

Another advantage of having such a research category is that the public and, to an extent, the health professions see research as a phenomenon apart and remote from their influence. The output of the research effort as well as its direction and support appear to be far-removed from meaningful intervention. A designated category for research in the public interest with procedures for public representation and involvement should help change these perceptions. The chances for a "tangible" public education and information effort should be greatly improved by specifying the public's own direct benefit as the basis for its continued involvement. And since the questions to be answered in public interest research can only be answered with public involvement—here biologicals are a superb example—the public can be held accountable for continued support. If community-oriented field trials are to be conducted regularly and if in-use surveillance of biologicals is to be productive, the public must

volunteer interest and participation. The community as an epidemiologic laboratory is already an established scientific concept; it should become a regular feature of research efforts in behalf of the public(*10*).

A third advantage of identifying a category of research in the public interest is its resulting in procedures by which the public or the community could truly participate in the research effort. Whether this would be by appointing or electing or otherwise identifying community persons or groups is possibly less important than that they be committed to their responsibilities and adequately informed as to the technical aspects of their assignments. They would serve as advocates, constructive critics, or "informed outsiders," to borrow Barber's terminology(*11*). They would address matters of protocol development, review, approval, and consent for all phases of the research on behalf of the community. They would promote participation among their constituents for efforts deemed to be in the public interest. They would assist in ruling on claims of injury to the environment or to people of the community as the result of community-wide research efforts, referring them for arbitration or litigation. In general, they would provide public viewpoints on all aspects of public interest research.

One easily can broaden the concept of research in the public interest from a community orientation to one of national or international dimensions. Obvious are the enhanced opportunities for scientific achievement from collaborative research on biologicals where data from standardized protocols of research or surveillance implemented under controlled conditions extend the base of experience. More precise understanding of effectiveness, safety, and community value are bound to result.

This review cannot fully explore the complexities in implementing our recommendation on public interest research. Nevertheless, there are a few obvious starting points. One is to "popularize" the concept among the health research community and among legislators, administrators, and the public itself. Guidelines, regulations, and legislation which influence research among human subjects should distinguish this category of effort from others and deal with its special requirements. Codes of ethics governing the involvement of human subjects in research should be considered for revision to address the distinctiveness of research with communities from that with individuals; and, furthermore, they should clarify the justifications for the research effort.[a] The visual, auditory, and written media should help the professions and the public recognize the merits of research for the public good and regularly reinforce the need for their active involvement.

These recommendations are all too global for reformation of well-established attitudes and practices. They may be sufficient to challenge them. We believe that a valuable contribution can be made toward securing health as a public good of the future when the concept of research in the public interest is actively discussed by groups like that conferring here on the issues of the community and the individual in biologicals research, development, and use. If the conclusions of this conference can distinguish the biologicals effort now and in the future from research generally, a significant step forward will have been taken.

[a] It, perhaps, should not be surprising that public good as an objective of biomedical research or medical care has received little attention in the past. Only two codes that deal directly or indirectly with research among humans mention public good as an objective or an outcome. One is Percival's Code (1803) in which innovative remedies and new methods of surgical treatment are justified on the basis of the public good(*12*). The other is the Nuremberg Code (1946-49) in which one of its ten points indicates that "the experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature."(*13*) The remaining dozens of codes, guidelines, and declarations referenced as the basis for the ethics of biomedical science focus entirely on research as clinical or therapeutic and carried out in individual patients or other research subjects.

SUMMARY

Evolution of the "biologicals enterprise" has been primarily influenced by scientific and sociocultural factors. Most important have been the need for safely and effectively controlling or preventing human disease, the scientific and technical possibilities for developing biologicals, and the acceptance of products as being valuable for routine use. It has generally been recognized that the community derives a benefit when biologicals are used, but a major strategy of biologicals research, development, and use in the past has focused on individual protection. In the future the biologicals enterprise will need increased public recognition that biologicals are essentially public resources, and as such require public encouragement, involvement, and support.

One way to focus attention on the public's investment in research in its own behalf, we believe, is to designate as a special category of research, "research in the public interest." To fully realize the potential of public interest research on biologicals, ways must be found to dramatize the knowledge that biologicals result in better health for communities as well as for individuals and that public participation in some phases of the biologicals effort is essential to continued progress.

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